Docket No.: 4518-0110PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Thomas FELZMANN

Application No.: 10/527,679 Confirmation No.: 7223

Filed: February 3, 2006 Art Unit: 1646

For: USE OF DENDRITIC CELLS (DCS) EXPRESSING INTERLEUKIN 12 (IL-12) Examiner: X. Xie

DECLARATION UNDER 37 C.F.R. § 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Wilfred Germeraad of the Department of Internal Medicine, Division of Haematology, Maastricht University Medical Center, the Netherlands, do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am an Assistant Professor at the Maastricht University Medical Center and have worked in immunology since 1988 and in this field since 1998.

I am familiar with U.S. patent application 10/527,679, as well as the activity of application of dendritic cells in cancer immune therapy.

I have read and understand the subject matter of the Office Action of March 3, 2010.

The following comments are offered in support of the patentability of the instant invention.

1. General comments

The Trivax technology platform was filed in patent application in 2002. Specifically, the Trivax technology is a method for the treatment of a tumor comprising administering an effective amount of Dendritic cells (DC), that are tumor specific and secrete IL-12, which are prepared by a process of (a) collecting DC or DC precursor cells from a suitable source to obtain a DC culture, (b) loading the DC with a tumor specific antigen, and (c) exposing the DC culture to a concentration of LPS and a concentration of IFN-γ effective to trigger the DC to secrete IL-12, wherein the exposure of LPS and IFN-γ occurs over a period of 2-6 hours.

This technology was at the time of filing a step in an entirely new direction of DC cancer immune therapy. It was the first such strategy that suggested the therapeutic use of antigen-charged DCs exposed to LPS/IFN-γ for enabling secretion of IL-12, a critical mediator of killer cell mediated immune responses.

1.1. Critical features of the Trivax technology platform

1.1.1. IL-12 secretion during DC/T-cell interaction

The most critical feature of the Trivax technology platform is that the DCs are enabled to secrete IL-12. This is accomplished by exposure of the DCs to the TLR4 ligand LPS in the presence of IFN-γ. IL-12 is the critical factor for type 1 polarization of an immune response. It supports the differentiation of helper T-cells into Th1 cells, which are characterised by IFN-γ secretion that enables cytolytic immunity mediated by CTLs.

When a DC and T-cell interact they form an immunological synapse [Davis, Nature Reviews, (2009) 9:543-553]. The immunological synapse is stabilized by adhesion molecules facilitating interaction of antigen presenting MHC molecules with TCRs. Signaling molecules secreted from the DC are most active when released directly into the immunological synapse, as only under these conditions the local concentration reaches a magnitude sufficient to transmit a signal of adequate strength. Molecules secreted outside the immunological synapse will

immediately diffuse into the surrounding tissue thus diluting the concentration of this molecule to levels that are not capable of signal transduction.

Importantly, IL-12 is released from an LPS/IFN-γ exposed DC for only about 24 hours [Kalinski, J. Immunol. (1999) 162: 3231-3236; Langenkamp, Nature Immunol., (2000) 1(4): 311-316]. To allow IL-12 to act on a T-cell during antigen presentation for a sufficiently long time it needs to be inoculated early during the 24 hour time window of IL-12 secretion [Felzmann, Cancer Immunol. Immunother. (2005) 54: 769-780; Hüttner, Cancer Immunol. Immunother. (2005) 54: 66-77]. The Trivax technology therefore requires a brief exposure to LPS/IFN-γ initiating a maturation program in the DC that follows its natural course even after removal of the stimulatory agents. None of the cited references suggest or would motivate one of skill in the art to provide limited exposure in that specific time window. Obviously, after inoculation into a patient there is no way of maintaining the soluble molecules LPS and IFN-γ in the vicinity of the DCs. Ultimately it was demonstrated that LPS and IFN-γ could be removed after 6 hours in vitro exposure without disrupting the maturation process of the DCs [Dohnal, J. Cell. Mol. Med. (2009) 13(8B):1741-1750].

Most importantly, IL-12 secretion was not impaired in DCs when LPS/IFN-γ was withdrawn in comparison with DCs that were cultured continuously in the presence of the maturation agents. This was the prerequisite for an inoculation of Trivax after 6 hours maturation and hence for a DC/T-cell interaction during the time window of IL-12 secretion [Dohnal, Cytotherapy (2007) 9(8): 755-770]. In contrast to IL-12, the cytokine IL-10 is produced for longer than 24 hours from DCs and will therefore become the dominant cytokine. Importantly, IL-10 will not support type 1 polarization of T-cells but will rather trigger the differentiation of immune suppressive regulatory T-cells.

Many institutions have used DCs for immune therapy [Steinman, Nature (2007) 449: 419-426]. Although the Trivax technology was published several years ago only a few institutions, including ours [see Vanderlocht et al., Int J Immunopathol Pharmacol. 2010 Jan-Mar; 23(1):35-50, but then FMKp instead of LPS is used], have adopted the concept of applying DCs only a few hours after exposure to a maturation stimulus to take advantage of the CTL cell activating effects of IL-12. This indicates that this strategy, which is at the core of the Trivax technology platform [Felzmann, 2005; Hüttner, 2005], was not obvious at the time of filing the

patent application and still is not considered obvious. In fact, many tumor immunologists questioned the necessity of IL-12 during T-cell stimulation for anti-tumor immune therapy. This is exemplified in a PubMed search conducted in January 2010 that yielded 1174 references containing the search terms "dendritic cell" and "clinical trial". Only 14 of these papers cross-reference with the search terms "LPS" or "lipopolysaccharide". On closer inspection of these few papers it becomes clear that only one group of investigators other than the group of the patent applicants [Dohnal, 2007] used LPS exposed DCs [Czerniecki, Cancer Res. (2007) 67(4):1842-1852].

Of course this may also mean, that the concept is not feasible for therapeutic purposes. However, in the patent application and in subsequent publications compelling evidence was provided that cytolytic immunity is indeed triggered by DCs manufactured according to the Trivax concept in vitro as well as in vivo [Felzmann, 2005; Hüttner, 2005; Dohnal, 2007; Dohnal, 2009].

1.1.2. Use of LPS in a clinical situation

LPS represents bacterial endotoxin that is the main mediator of the severe symptoms of a septic situation in a generalised bacterial infection. Although in sepsis research LPS is used in healthy volunteers for investigating it's in vivo effects [Suffredini, J. Infectious Diseases (1999) 179: 1278-1282], many immunologists consider LPS too dangerous to be applied to humans even in trace amounts.

Consequently, although under the search term "dendritic cell" the NIH's www.clinicaltrials.gov platform lists 308 clinical trials exploring the use of DC immune therapies in January 2010, only 2 listings cross-reference with the search term "LPS" and 22 listings with the search term "endotoxin". Actually, only 32 of these more than 300 listings for DC clinical trials cross-reference with the search terms ""mature" or "maturation" indicating that about 90% of clinical trials that investigate DCs for cancer treatment do not expose them to any maturation agent. More commonly used maturation agents are "CD40*" (7 listings), "TNF" (8 listings), and "CpG" or "polyIC" (4 listings), two other TLR ligands that have a similar effect on DCs as the interaction of LPS with its ligand TLR4. This clearly shows that although many DC

immune therapy trials have been conducted, few investigators found it obvious or even feasible to use LPS for DC maturation in a clinical situation.

1.2. Conclusion

This review of the state of the art demonstrates beyond any reasonable doubt that it does not appear obvious to use DCs a few hours after exposure to a maturation stimulus to take advantage of the time window of IL-12 secretion, or to use LPS as a maturation agent. Otherwise, it seems that many more investigators would have adopted that strategy.

2. Specific comments

2.1. Kalinski et al.

2.1.1. Maturation time

Kalinski et al. [Kalinski, 1999] reported that IL-12 is secreted only during the first 24 hours after exposure to a CD40/CD40L mediated signal in the presence of IL-1β and TNF-α. At no point in their paper they demonstrate or even suggest a similar time dependence for DCs exposed to LPS/IFN-γ. The molecules involved in the CD40/CD40L signaling pathway [Luo, J. Clin. Inv. (2008) 115(10): 2625-2692] are entirely different from the molecules that are involved in the LPS signaling pathway (Figure 1). Hence, it is not obvious that a CD40/CD40L mediated signal will have the same effect on IL-12 secretion from DCs as an LPS mediated signal. Actually, it is even surprising that two entirely different signaling pathways would result in the same effect on IL-12 secretion. In another respect, the two signaling pathways are clearly different: mature DCs are still responsive to a CD40/CD40L mediated signals, whereas they become resistant to an LPS mediated signal [Dohnal, J. Cell. Mol. Med. (2009) 13(1): 125-135].

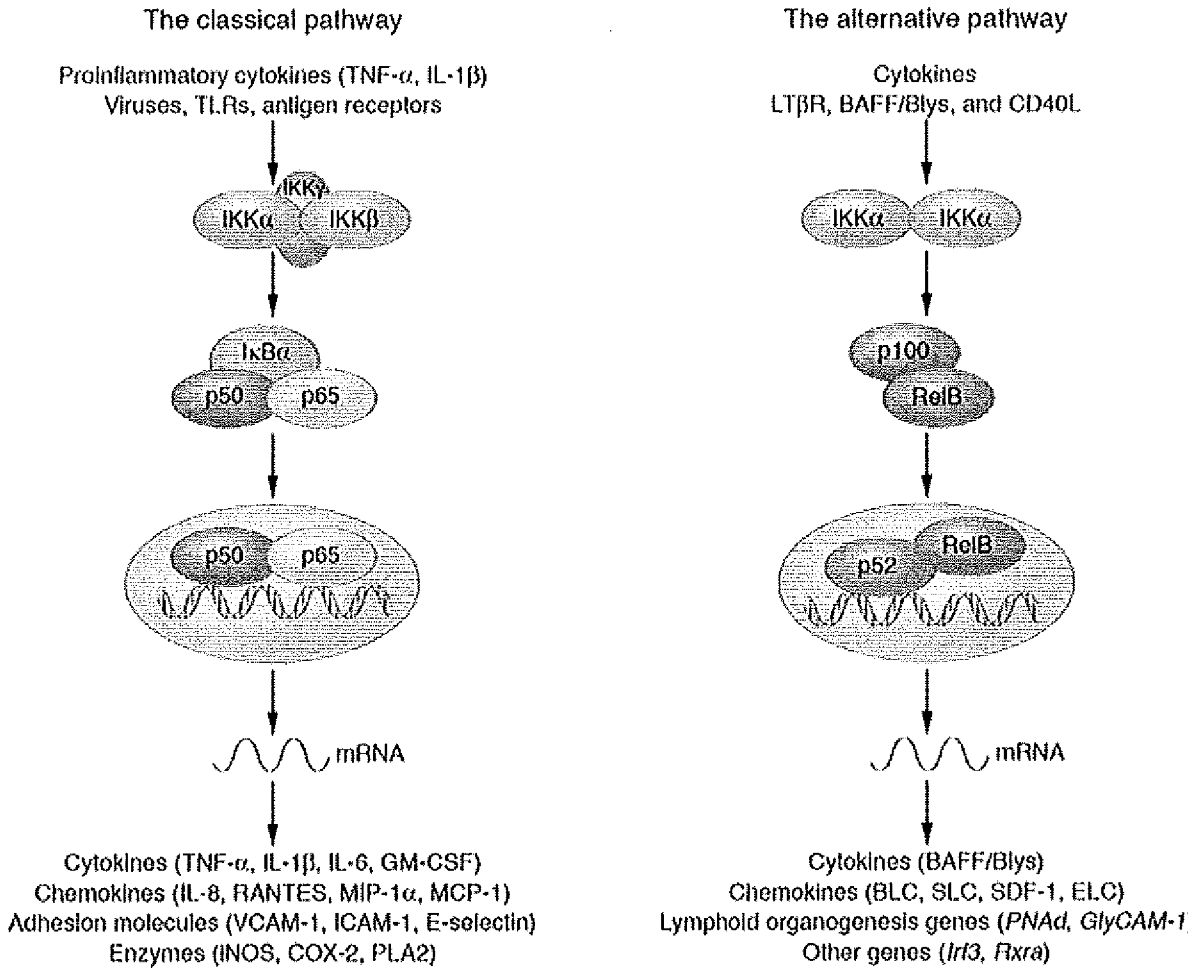

Figure 1: IKK/NF-κB signaling pathways [Luo, 2005]. The classical pathway is activated by a variety of inflammatory signals, resulting in coordinate expression of multiple inflammatory and innate immune genes. The alternative pathway is strictly dependent on IKKα homodimers and is activated by lymphotoxin β receptor (LTβR), B-cell activating factor belonging to the TNF family (BAFF), and CD40L. The alternative pathway plays a central role in the expression of genes involved in development and maintenance of secondary lymphoid organs, such as BLC, B-lymphocyte chemoattractant; ELC, Epstein-Barr virus-induced molecule 1 ligand CC chemokine; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; PLA2, phospholipase A2; SDF-1, stromal cell–derived factor-1α; SLC, secondary lymphoid tissue chemokine.

The CD40/CD40L mediated signal with or without IFN-γ was not applied to immature DCs but rather to DCs that were already induced to mature by IL-1β/TNF-α or LPS.

This is in stark contrast to the Trivax technology, which contacts immature DCs that have not received any other maturation stimulus with LPS/IFN-γ. It therefore has to be concluded that the effects on IL-12 secretion from DCs observed by Kalinski et al. are the result of a combination of maturation stimuli that involve IL-1β/TNF-α or LPS and CD40/CD40L. (Kalinski, page 3232, col. 1, line 44-48, and legend to Figure 3). Figure 3B of Kalinski et al. shows IL-12 secretion of DCs but does not support any conclusions concerning the time dependence of IL-12 secretion from immature DCs exposed to LPS/IFN-γ for 6 hours.

Of particular significance is that in the Trivax technology the maturation agents LPS and IFN-γ are removed after 6 hours from the DCs [Felzmann, 2005; Hütterr, 2005]. Kalinski et al. did not explicitly show that the maturation of DCs continues unperturbed even after removal of LPS/IFN-γ. This feature is critical, as DCs after inoculation into a patient will no longer have contact with the LPS/IFN-γ supplemented culture medium. In general, therefore, in vitro experiments that are based on the continuous presence of the maturation agents in cell culture media do not deliver any useful information concerning the in vivo situation.

2.1.2. Killer cell activity

Kalinski et al. do not study the induction of killer cell activity from DCs. They do not even mention the effect of DCs on the activation of killer cells. In contrast, it was clearly demonstrated that DCs manufactured and used according to the Trivax technology platform induce killer cell activity [Felzmann, 2005; Hütterr, 2005]. Thus, Kalinski et al. would not make obvious to one of skill in the art the use of DCs for the treatment of diseases such as cancer or viral infections for which purpose the activation of killer cells is of critical importance.

2.1.3. Antigen loading

In the last paragraph of their paper, Kalinski et al. refer to the potential of using DCs in a therapeutic capacity (Kalinski, 3235, col. 2, last full paragraph). However, they specifically call into question whether such an approach is feasible as foetal calf serum (FCS) free cultures would have to be used and at the time it was not clear whether any of their observations would hold true

under such circumstances. Furthermore, from the overall theme of the paper it is reasonable to conclude that this statement relates to the therapeutic use of DCs after exposure to a CD40/CD40L mediated signal. In contrast, it is very unlikely that they aimed this statement at LPS matured DCs.

2.1.4. Conclusion

The paper by Kalinski et al. clearly aims at investigating the effect of CD40/CD40L mediated signals on IL-12 secretion in DCs that are pre-matured with IL-1β/TNF-α or LPS <u>without</u> IFN-γ. There is not a single reference in the entire paper that indicates that the activity of IL-12 secretion in DCs exposed to LPS/IFN-γ might have a time related activity comparable to DCs receiving a CD40/CD40L mediated signal. Thus, it is clearly not obvious to conclude from Kalinski et al. the use of LPS/IFN-γ exposed IL-12 secreting DCs in a therapeutic capacity.

2.2. Bosch

2.2.1. T-cell immune therapeutic

The invention of Bosch aims at manufacturing T-cells in vitro that are type 1 polarized. In claims 36-40, the T-cells will be administered to an animal or human after in vitro co-cultivation with DCs. There appears to be no intention of using DCs in the capacity of an anti-tumor immune therapeutic.

2.2.2. Exclusive use of 24 hours DCs

In paragraph 63 and again in paragraph 78, Bosch mentions that immature DCs were contacted with BCG and IFN-γ for 24 hours. The claims section does not specify for how long a DC has to be exposed to the maturation agent and one has therefore to assume that the claims are based on DCs matured for 24 hours. All examples use such DCs to trigger T-cell responses.

Again, it is critical to realize that IL-12 is produced from DCs for less than 24 hours after exposure to any maturation agent including microbial signals such as those delivered from LPS

or BCG but also after receiving a CD40/CD40L mediated maturation signal [Kalinski, 1999; Langenkamp, 2000]. Therefore, if DCs are matured first for 24 hours or longer and than co-cultivated with T-cells, no more IL-12 production may be detected. Therefore, the claim of Bosch that the observed beneficial effect on T-cell stimulation is due to IL-12 is unsustainable.

The observations may be due to an in vitro artifact: the IL-12 protein secreted from the DCs remains inside a culture vessel and accumulates during the first 24 hours in the cell supernatant. In an organism, the IL-12 released from a DC immediately diffuses away. The microenvironment of the DC/T-cell interaction and the immunological synapse is devoid of IL-12 and no IL-12 mediated immune modulation is possible. If T-cells are added to a culture of DCs that had the chance to accumulate IL-12 for 24 hours in the supernatant, effects may be observed that might be attributed to accumulated but not freshly secreted IL-12 and which in vivo would never occur 24 hours after exposure to the maturation stimulus. Hence, the method demonstrated by Bosch follows exactly the state of the art at the time of publication: it was the general practice to expose DCs to a maturation stimulus for 24-48 hours.

Particularly when DCs are used in the capacity of a cancer vaccine one needs to take into consideration the time dependent IL-12 secretion. If a DC cancer vaccine is applied to a patient 24 hours or later after receiving the maturation signal, an interaction of DCs with T-cells in vivo has necessarily to take place in the absence of IL-12 and therefore, immune modulation by IL-12 in vivo will not correspond to observations in vitro. In addition, and as outlined above, DCs need to continue their maturation program triggered by LPS/IFN-γ even after removal of these reagents after 6 hours. No such demonstration is available except in the experiments leading to the Trivax technology [Felzmann, 2005; Hüttner, 2005].

2.2.3. Conclusion

The invention of Bosch aims at using DCs not in a therapeutic capacity but rather for in vitro priming of T-cells. This makes it an entirely different technology that is not comparable to the direct use of DCs in immune therapy. In addition, as everybody else, Bosch uses DCs that have lost the capacity to secrete IL-12, which is the central and still unique characteristic of the Trivax technology platform.

3. Summary

In hindsight, it may seem obvious to use IL-12 secreting DCs but at the time of filing this patent application this was a radical innovation as no other group had applied the kinetic of IL-12 secretion to the design of a DC immune therapeutic. In fact, as outlined in the introduction, even now the field of tumor immune therapy has not adopted this strategy. This was and is further enforced by the common belief that it would be impossible to use endotoxins in a therapeutic situation.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: April 20, 2010

Dr. Wilfred Germeraad

CURRICULUM VITAE

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Place of birth	Rotterdam
Date of birth	2 March 1962
Nationality	Dutch
Marital status	married, 2 children

WORK / RESEARCH EXPERIENCE

2009-present **Assistant Professor**

2003-2009 **Senior Research Staff, Immunologist,** Department of Internal Medicine, Division of Haematology, Maastricht University Medical Center, Maastricht, the Netherlands

Subject Division: Immunotherapy

- Dendritic cells for tumour vaccine development
- De novo generation of T cells for adoptive transfer

Responsibilities:

- Development and execution of research projects
- Managing a group of 6-10 people, including development and education
- Fundraising
- Departmental Biosafety Expert
- Departmental Computer Expert
- FACS Unit supervision
- Member of the Workgroup Immunology Maastricht
- Coordinator "SMBWO Immunologist" certification in Maastricht
- Member of various teaching course coordination groups
- Teaching graduate and undergraduate students

2000-2003 **Teamleader**, U-BiSys and Crucell, Leiden, the Netherlands

Subject Team: Targeting Dendritic cells for tumour vaccine development

Responsibilities:

- Development and execution of research projects
- Managing group of 6 - 9 people, including development and education
- Creating Intellectual Property
- Translating Research into Business Development
- Setting up of international collaborations
- Scientific Data Management

1998-1999 **Senior Scientist**, U-BiSys, Department of Immunology, University Medical Center Utrecht, Utrecht, the Netherlands
Subject: Molecular aspects of human dendritic cell differentiation

- Setting up of Representational Difference Analysis Technology
- Supervision of 3 undergraduate students
- Organizing many lab related practical matters

04 - 08 / 1996 **Guest Researcher**, Department of Immunology, University Hospital Utrecht, the Netherlands.
Subject: Development of monoclonal phage antibodies.

1996-1997 **Postdoctoral Fellow**, Department of Immunology, Erasmus University Rotterdam, the Netherlands.
Subject: The role of the thymic stroma in T cell differentiation

- Setting up Phage Antibody Display Technology and related labs (VMT)
- Supervision of foreign graduate student

1994 - 1996 **Postdoctoral fellow**, Department of Pathology, Childrens Hospital Los Angeles, Los Angeles, CA, USA
Subject: Transgenic and knock-out animal models for Philadelphia chromosome positive leukemia

1988 - 1994 **PhD Student**, Department of Immunology, Kyoto University, Kyoto, Japan
Dissertation: Retroviral gene transfer into hematopoietic stem cells

Defended on 23 July 1994

EDUCATION

1980 - 1987 Medical Biology, Free University Amsterdam, Netherlands
Subjects: Human Genetics, Oncology
Main Subject: Immunology

2010 Registration Immunologist (SMBWO)

COURSES

01 / 2010	Coaching
01 / 2010	Radiation Hygiene Refreshment course: PET imaging
06 / 2009	Oral examination
04-09 / 2009	Medical Immunology
09 / 2008	Knowledge Valorisation / Patent application
09/07-06/08	BKO, Basic Teaching Qualification
10 / 2004	Radiation Hygiene Refreshment course
11-12 / 2003	Animal Science (Art. 9)
09 / 2003	Problem Oriented Education
09 / 2003	Basic Tutor Training
12 / 2001	Vector NTI (DNA analysis)
11 / 2001	Communication skills and conversation techniques
09-12 / 1986	Biology education (received teacher's license 1st degree)
11 / 1983	Working with radioactivity and liquid scintillation (B4)

TEACHING EXPERIENCE

- Daily supervision over PhD students (7) and undergraduate students in scientific internships (18)

- Organizing Education:

  Block coordinator "Molecular Diagnostics and Therapy" of Clinical Molecular Sciences Master
  2009

  Co-Block coordinator "Attack and Defense" for sophomores in Molecular Life Sciences 2009

  Module coordinator in "Cancer" Module of Clinical Molecular Sciences Master 2007, 2008, 2009

  Member of the planning group "Abdomen" module phase 1 in A-KO master

  Responsible for KO-part
  2008, 2009, 2010

  Vice-coordinator of the planning group "Scientific internship" phase 2 in A-KO master 2008, 2009, 2010

  Member of the planning group "Combi Internship" phase 4 in A-KO master 2008, 2009, 2010

Teaching courses:

- Course "Abdomen" Phase 1 A-KO master, Maastricht
  04 – 06 / 2009, 2010
  Coach, lectures, discussion groups
- Course " Attack and Defense" for sophomores in Molecular Life Sciences Maastricht 02 – 04 / 2006-2010
  Tutor, lectures and/or discussion groups
- Course "Cancer" for Master's course students in Clinical Molecular Sciences TUL Maastricht/Diepenbeek 11 / 2005-2009
  Lectures and discussion groups
- Course "Autoimmune diseases and Autoimmunity" for sophomores in Medicine
  University Maastricht 06 / 2004-2009

lecture

- Course "Cell Growth" for sophomores in Medicine
  University Maastricht 09/10 2003-2008
  Chosen by students as best tutor of University (3rd place) in 2004/2005
  Tutor

Teaching during previous employment:

- Course "Essential Immunology, Roitt" for technicians
  Crucell 03 / 2002 – 12/2002
- Course "Immunology" for juniors in Biomedical Sciences
  Utrecht University 02 / 2002
- Course "Infection and Immunity" for freshman in Medicine,
  Utrecht University 04 / 2000 – 05 / 2000
- Practical course "Immunohistochemistry" for AOI's, Erasmus University
  Rotterdam 10 / 1997
- Practical course "Basic Histology" for freshman in Medicine, Erasmus
  University Rotterdam 02 / 1997 – 04 / 1997

- Memberships - Dutch Society of Immunology
  - Dutch Society of Biotechnology
  - Dutch Society for Biology
  - Dutch Society for Biochemistry and Molecular Biology
  - Japanese Society of Immunology (1988-1994)

- Member of the Scientific Advisory Board for the Maastricht Medical Students
  Research Conference 2009, 2010

- Computer skills: include Text, Powerpoint, Excel, DNA analysis, FACS
  analysis, Websites, NuGenesis data base management; Macintosh and
  Windows OS
  Departmental computer expert Maastricht 10 / 2005 - present

CO-PROMOTOR OF PhD STUDENTS

- S. Cloosen: Dendritic cells, Mucin-1 and cancer vaccines
  University of Maastricht, November 23, 2006

RESEARCH AWARDS

- Poster Price for:
  Adoptive T cell therapy for patients undergoing HSC-transplantation. Annual meeting of the Dutch society for Immunology. Noordwijkerhout, the Netherlands 12 / 2008
- Poster Price for:
  Tumor associated antigen mucin-1 is expressed on mTECs, possible implications for tumor vaccination. International Rolduc Workshop on T Cell Biology, Kerkrade, the Netherlands. 05 / 2004

- Science and Technology Postdoctoral fellowship from the European
  Community 04 / 1993 – 03 / 1994

- Predoctoral fellowship from Monbusho, Japanese Ministry of Education 04 / 1989 – 03 / 1993
- Visiting research fellowship for foreign students from Monbusho, Japanese Ministry of Education 01 / 1988 – 03 / 1989

GRANTS AWARDED

- GMP production of T/NK cell progenitors to enhance immune reconstitution of patients after haploidentical stem cell transplantation €552.200
  WTV Germeraad, B Meek and GMJ Bos
  KWF – Dutch Cancer Foundation 2010
- Development of cancer immunotherapy €100,000
  E. Stalmeijer, WTV Germeraad
  Limburgs Stimulation Fund Cell therapy 2007
- Development of cancer immunotherapy and stem cell therapy based on an artificial thymus technology platform €1,000,000
  WTV Germeraad, GMJ Bos, J Thio and R Lardenoije
  Technical Develoment grant Dutch Ministry of Economic Affairs 2006
- Generation of tumor specific T cells against Mucin-1 positive tumours by use of Dendritic cells €125,000
  GMJ Bos and WTV Germeraad
  Profileringsfonds AZM 2005
- Developing tumor vaccines through dendritic cell targeting
  WTV Germeraad €150,000
  EU / Marie Curie Industry Host Fellowship 2002
- Innovative treatment of Langerhans Cell Histiocytosis: production and functional analysis of 6 fully human monoclonal antibodies against CD1a derived from a phage antibody display library. $100,000
  WTV Germeraad, RM Egeler, T Logtenberg and M van Meijer
  Histiocytosis Society of America 2001
- Clonotypic single chain antibodies to islet specific T cells in auto-immune diabetes
  W van Ewijk and WTV Germeraad fl 367,000
  Diabetes Fonds Nederland 1998

TEACHING AWARDS

- Second runner-up best tutor of University Maastricht Year 2004-2005

REVIEWER/EDITORIAL

- Managing Editor Rhinology
- Reviewer for: Cancer Letters, International Journal of Cancer, Gene Therapy, Stem Cells, Human Gene Therapy, Immunology Investigations, J Controlled Release, Acta Histologica, Journal of Dermatological Science, International Immunology, Cellular Reprogramming
- Grant reviewer: Israel Science Foundation

PATENTS

Germeraad WTV, Lekkerkerker AN, Logtenberg T. Antigen presenting cell targeting conjugate, an Antigen presenting cell contacted with such conjugate, Their use for vaccination or as medicament, and Methods for their production or generation.
Application date: November 30, 2001.

Germeraad WTV, van Meijer M, Throsby M, Arceci R and Kruisbeek AM. Human monoclonal antibodies against CD1a.
Application date: July 1, 2002.

LIST OF PUBLICATIONS

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2. Limpens J, van Meijer M, van Santen HM, Germeraad WTV, Hoeben-Schornagel K, Breel M, Scheper RJ and Kraal G. Alterations in dendritic cell phenotype and function associated with immunoenhancing effects of subcutaneously administered cyclophosphamide derivates. Immunol. 73, 255 - 263, 1991.
3. Gyotoku J-I, El-FarrashM, Fujimoto S, Germeraad WTV, Watanabe Y, Teshigawara K, Harada S and Katsura Y. Inhibition of Human Immunodeficiency Virus replication in a human T cell line by antisense RNA expressed in the cell. Virus Genes 5, 3 ,189 - 202, 1991.
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5. Dou YM, Germeraad WTV, Gyotoku J-I and Katsura Y. Frequency analysis of the T cell precursors in the thymus. Cell. Immunol. 150, 269 - 280, 1993.
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7. Germeraad WTV, Asami N, Fujimoto S, Mazda O and Katsura Y. Efficient retrovirus-mediated gene transduction into murine hematopoietic stem cells and longlasting expression using a Transwell coculture system. Blood, 84, 3, 780 - 789, 1994.
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10. Gojo S, Kitamura K, Germeraad WTV, Yoshida Y, Niwaya K and Kawachi K. Ex vivo gene transfer into myocardium using replication-devective retrovirus. Cell Transpl. 5, S82-S84, 1996.
11. van Ewijk W, de Kruif J, Germeraad WTV, Berendes P, Ropke C, Platenburg PP en Logtenberg T. Subtractive isolation of phage-displayed single chain

antibodies to thymic stromal cells using intact thymic fragments. Proc. Natl. Acad. Sci, USA, 94, 9603-9609, 1997.

12. Germeraad WTV, deKruif J, Berendes P, Kuijpers H, Ramaekers FCS, Logtenberg T and van Ewijk W. Single chain antibodies detecting thymus stromal cells obtained by using thymic fragments as selective tissue. In: Antibody Engineering II: New technologies, applications and commercialisation, IBC library series, 5.7.1-5.7.5, 1997.
13. van Ewijk W, Wang BP, Hollander G, Kawamoto H, Spanopoulou E, Itoi M, Amagai T, Jiang YF, Germeraad WTV, Chen WF and Katsura Y. Thymic microenvironments, 3-D versus 2-D ? Sem. in Immunol. 1999.
14. van Ewijk W, Kawamoto H, Germeraad WTV, and Katsura Y. Developing thymocytes organize thymic microenvironments. Curr. Topics in Microbiol. and Immunol. 125-132, 2000.
15. Havenga MJE, Lemckert AAC, Ophorst OJAE, van Meijer M, Germeraad WTV, Grimbergen J, van den Doel MA, Vogels R, van Deutekom J, Janson AAM, de Bruijn JD, Uytdehaag F, Quax PHA, Logtenberg T, Mehtali M and Bout A. Exploiting the natural diversity in adenovirus tropism for therapy and prevention of disease. J Virol 76, 4612-4620, 2002.
16. Germeraad WTV, Kawamoto H, Itoi, M, Amagai T, Yiang YF, Katsura Y. and van Ewijk W. Development of unique three-dimensionally oriented thymic microenvironments requires T cell progenitors and a local high oxygen concentration. J Hist Cytochem 51: 1225-1235, 2003.
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